Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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SUPPLEMENTARY APPENDIX FOR THE EMPEROR-PRESERVED TRIAL

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operation with representatives from Boehringer Ingelheim, who were also represented in the executive committee of the trial.

The executive committee developed and amended the protocol, case report forms, and statistical analysis plan; oversaw the recruitment of patients and the quality of follow-up; supervised the analysis of data; and the academic members provided an independent interpretation of the results. An independent statistician replicated and verified the analyses. The corresponding authors, who had unrestricted access to the data, prepared the drafts of the manuscript, which were then reviewed and edited by all authors, including representatives of Boehringer Ingelheim.

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KEY INCLUSION AND EXCLUSION CRITERIA

Key Inclusion criteria

- Age ≥18 years at screening. For Japan only: Age ≥20 years at screening
- Male or female patients. A woman is considered of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information
- Patients with chronic HF diagnosed for at least 3 months before Visit 1 (Screening), and currently in HF NYHA class II-IV
- Chronic HF with preserved EF defined as LVEF >40% per local reading (obtained under stable conditions by echocardiography, radionuclide ventriculography, invasive angiography, MRI or CT) and no prior measurement of LVEF ≤40% under stable conditions. A historical LVEF may be used if it was measured within 6 months prior to visit 1 and more than 90 days after any myocardial infarction (as defined in exclusion criterion No.1) or the LVEF may be measured after study consent has been obtained. The LVEF must be documented in an official report prior to randomization
- Elevated N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) >300 pg/mL for patients without AF, OR >900 pg/mL for patients with AF, analysed at the Central laboratory at Visit 1
- Patients must have at least one of the following evidence of HF: a. Structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) documented by echocardiogram at Visit 1 or within 6 months prior to Visit 1, OR b. Documented HHF within 12 months prior to Visit 1
- Oral diuretics, if prescribed to patient according to local guidelines and discretion of the Investigator, should be stable for at least 1 week prior to Visit 2 (Randomisation)
- Body Mass Index (BMI) <45 kg/m^2 at Visit 1 (Screening)
- Signed and dated written ICF in accordance with GCP and local legislation prior to admission to the trial

Key Exclusion criteria

Cardiovascular diseases or treatments that increase the unpredictability of or change the patients' clinical course, independent of heart failure

- Myocardial infarction (increase in cardiac enzymes in combination with symptoms of ischemia or new ischemic ECG changes), coronary artery bypass graft surgery, or other major cardiovascular surgery, stroke or transient ischemic attack in past 90 days
- Heart transplant recipient or listed for heart transplant. Currently implanted left ventricular assist device.
- Cardiomyopathy based on infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. hemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction.
- Any severe (obstructive or regurgitant) valvular heart disease, expected to lead to surgery during the trial period
- Acute decompensated heart failure requiring intravenous diuretics, vasodilators, inotropic agents or mechanical support within 1 week of screening and during the screening period prior to randomization
- Implanted cardioverter defibrillator within 3 months prior to screening
- Cardiac resynchronization therapy

Untreated or undertreated cardiovascular conditions that might influence the course of heart failure or tolerability of the study medications

- Atrial fibrillation or atrial flutter with a resting heart rate >110 bpm documented by ECG at screening
- Systolic blood pressure ≥180 mmHg at randomization. If the systolic blood pressure is 151-179 mmHg, the patient should be receiving ≥3 antihypertensive drugs
- Symptomatic hypotension and/or a systolic blood pressure <100 mmHg at screening or at randomization

Significant comorbid conditions that might influence the clinical course, independent of heart failure

- Chronic pulmonary disease requiring home oxygen, oral corticosteroid therapy or hospitalisation for exacerbation within 12 months; significant chronic pulmonary disease; or primary pulmonary arterial hypertension
- Acute or chronic liver disease, defined by serum levels of transminases or alkaline phosphatase more than three times the upper limit of normal at screening
- Impaired renal function, defined as eGFR < 20 mL/min/1.73 m^2 (CKD-EPI) or requiring dialysis at the time of screening
- Hemoglobin <9 g/dL at screening
- Major surgery (major according to the investigator's assessment) performed within 90 days prior to screening, or major scheduled elective surgery (e.g. hip replacement) within 90 days after screening.
- Gastrointestinal surgery or gastrointestinal disorder that could interfere with trial medication absorption.
- Any documented active or suspected malignancy or history of malignancy within 2 years prior to screening, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix, or low risk prostate cancer (patients with pre-treatment PSA <10 ng/mL, and biopsy Gleason score of ≤6 and clinical stage T1c or T2a)
- Presence of any other disease than heart failure with a life expectancy of less than one year (in the opinion of the investigator)

Any condition that might jeopardize patient safety, limit the patients' participation in the trial, or undermine the interpretation of trial data.

- Current use or prior use of a SGLT2 inhibitor or combined inhibitor of SGLT1 and SGLT2 within 12 weeks prior to screening or randomization. Discontinuation of a SGLT2 inhibitor or combined inhibitor of SGLT1 and SGLT2 inhibitor for the purposes of study enrolment is not permitted.
- Known allergy or hypersensitivity to any SGLT2 inhibitors
- History of ketoacidosis
- Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial
- Currently enrolled in another investigational device or drug study or are less than 30 days since the completion of a trial of another investigational device or drug study. Any patient receiving any investigational treatment other than the study medications for this trial.
- Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, will make the patient unlikely to fulfill the trial requirements or complete the trial
- Women who are pregnant or are nursing or who plan to become pregnant while in the trial
- Any other clinical condition that would jeopardize patient safety while participating in this trial or may prevent the subject from adhering to the trial protocol

MAJOR PROTOCOL-SPECIFIED EFFICACY ENDPOINTS

Primary endpoint

The composite of time to first event of adjudicated cardiovascular death or adjudicated hospitalization for heart failure

The individual components of the primary endpoints, i.e., time to first hospitalization for heart failure and time to cardiovascular death

Secondary endpoints included in hierarchical testing

1. Total (first and recurrent) adjudicated hospitalizations for heart failure
2. Slope of estimated glomerular filtration rate (GFR)

Other prespecified endpoints not included in hierarchical testing

Other secondary endpoints (not included in testing hierarchy are the following:

1. Composite renal endpoint, defined as time to first occurrence of (1) chronic dialysis; (2) renal transplantation; (3) sustained reduction of ≥40% in estimated GFR; or (4) sustained estimated GFR <15 mL/min/1.73 m^2 for patients with baseline estimated GFR ≥30 mL/min/1.73 m^2 or <10 mL/min/1.73 m^2 for patients with baseline eGFR <30 mL/min/1.73 m^2

Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days. An estimated reduction in GFR is considered sustained, if it is determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days

2. Change from baseline in clinical summary score (heart failure symptoms and physical limitations domains) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) at week 52

3. Total (first and recurrent) hospitalizations for any reason

4. Time to all-cause mortality

5. Time to onset of diabetes (defined as HbA1c ≥6.5% or as diagnosed by the investigator) in patients with prediabetes (defined as no history of diabetes, no prior HbA1c ≥6.5%, and a pre-treatment HbA1c of ≥5.7 and <6.5%)

ADJUDICATED OUTCOME EVENT DEFINITIONS

All cardiovascular endpoint definitions were modifications based on draft recommendations for CDISC August 20, 2014 (Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials for CDISC, Hicks KA et al August 2014) and included in the Clinical Endpoint Committee (CEC) Charter. The CEC Charter specified that in the case of limited or missing data, the committee was to adjudicate events based on their clinical expertise and the totality of the evidence.

Hospitalization for heart failure

A Heart Failure Hospitalization should include the following criteria:

1) The adjudicated primary diagnosis is admission to hospital for heart failure.
2) The patient's length-of-stay in hospital extends for at least 12 hours (or a change in calendar date if the hospital admission and discharge times are unavailable). Emergency room visit for ≥ 12 hours with intravenous therapy would be considered equivalent as admission to hospital.
3) The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:
    a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal dyspnea)
    b. Decreased exercise tolerance
    c. Fatigue
    d. Other symptoms of worsened end-organ perfusion such as dizziness, mental confusion or volume overload such as weight gain or lower extremity swelling.
4) The patient has objective evidence of new or worsening HF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including:
    a. Physical examination findings considered to be due to heart failure, including new or worsened:
        i. Peripheral edema
        ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
        iii. Pulmonary rales/crackles/crepitations
        iv. Increased jugular venous pressure and/or hepatojugular reflux
        v. S3 gallop
        vi. Clinically significant or rapid weight gain thought to be related to fluid retention
    b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
    c. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT proBNP) concentrations consistent with decompensation of heart failure. In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
    d. Radiological evidence of pulmonary congestion
    e. Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' >15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI) **OR**
    f. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg, central venous pressure ≥12 mmHg, or a cardiac index <2.2 L/min/m^2

5) The patient receives initiation or intensification of treatment specifically for HF, including at least ONE of the following:

a. Augmentation in oral diuretic therapy. NOTE: If the intensification is solely oral diuretics, the duration of hospitalization must be at least 24 hours.
b. Intravenous diuretic or vasoactive agent (e.g., inotrope, vasopressor, or vasodilator)
c. Mechanical or surgical intervention, including:
    i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
    ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis).

An endpoint heart failure hospitalization requires admission to the hospital for heart failure, worsening of symptoms of heart failure, a duration of hospitalization of at least 12 hours, the intensification of heart failure therapy, and a committee consensus that the hospitalization was primarily due to worsening heart failure. Changes in physical signs or laboratory tests, whenever available and documented, will be considered to be supportive.

Cause of death

Cause of death was adjudicated, as either Cardiovascular death or Non-Cardiovascular death. Cause of death was further categorized when possible.

Cardiovascular death includes the following categories:
1. Death due to Acute Myocardial Infarction: refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days after a MI related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia. We note that there may be assessable mechanisms of cardiovascular death during this time period, but for simplicity, if the cardiovascular death occurs ≤ 30 days of the myocardial infarction, it will be considered a death due to myocardial infarction. Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis.

Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI.

Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e. chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

2. Sudden Cardiac Death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:
    a. Death witnessed and occurring without new or worsening symptoms
    b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
    c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
    d. Death after unsuccessful resuscitation from cardiac arrest (e.g., implantable cardioverter defibrillator (ICD) unresponsive sudden cardiac death, pulseless electrical activity arrest)
    e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
    f. Unwitnessed death in a subject seen alive and clinically stable ≤ 72 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is noted to be alive ≤72 hours of being found dead, sudden cardiac death (criterion 2f) should be recorded. For patients who were not observed alive within 72 hours of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days).

3. Death due to Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

New or worsening signs and/or symptoms of congestive heart failure (CHF) may include any of the following:

- New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
- Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration
- Confinement to bed predominantly due to heart failure symptoms
- Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction or as the consequence of a primary event
- Cardiogenic shock, manifest as clinical signs and symptoms of hypoperfusion felt to be secondary to cardiac dysfunction, and not occurring in the context of an acute myocardial infarction or as the consequence of a primary arrhythmic event
- Patients who are hospitalized and are being actively treated for heart failure and who have a sudden death as the terminal event will be classified as having a heart failure related death.

4. Death due to Stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

5. Death due to Cardiovascular Procedures refers to death caused by the immediate complications of a cardiac procedure.

6. Death due to Cardiovascular Hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. Death due to Other Cardiovascular Causes refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

Non-cardiovascular death is defined as any death with a specific cause that is not thought to be cardiovascular in nature.

The following is a suggested list of non-CV causes of death:

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory (e.g., Systemic Inflammatory Response Syndrome (SIRS) / Immune (including autoimmune) (may include anaphylaxis from environmental (e.g., food allergies)

• Hemorrhage that is neither cardiovascular bleeding or a stroke
• Non-CV procedure or surgery
• Trauma
• Suicide
• Non-prescription drug reaction or overdose
• Prescription drug reaction or overdose (may include anaphylaxis)
• Neurological (non-cardiovascular)
• Malignancy
• Other non-CV causes

Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause.

Occasionally, it may not be possible to determine exact causality when 2 lethal conditions contribute to death equally. In this circumstance all events not due solely to non-CV causes should be adjudicated as CV-related.

All events for which there is "lack of information" (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death should be adjudicated as undetermined cause of death.

Myocardial Infarction (non-fatal)

General Considerations
The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post mortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

Criteria for Myocardial Infarction
a. Clinical Presentation
The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, heart failure, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.
b. Biomarker Elevations
For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be

used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. In general, troponins are preferred. CK-MB should be used if troponins are not available, and total CK may be used in the absence of CK-MB and troponin.

c. Electrocardiogram (ECG) Changes
Electrocardiographic changes can be used to support or confirm a MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.
• ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):

- ST elevation New ST elevation at the J point in two contiguous leads with the cut-points:
  - ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply:
    - ≥0.2 mV in men ≥40 years (≥0.25 mV in men <40 years)
    - or ≥0.15mV in women.
- ST depression and T-wave changes:
  - New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or new T inversion ≥0.1 mV in two contiguous leads with prominent R wave or R/S ratio >1.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

• Criteria for pathological Q-wave

- Any Q-wave in leads V2-V3 ≥0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, and aVF)

The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

• ECG changes associated with prior myocardial infarction

- Pathological Q-waves, as defined above
- R-wave ≥0.04 seconds in V1-V2 and R/S ≥1 with a concordant positive T-wave in the absence of a conduction defect

• Criteria for prior myocardial infarction
Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q-waves with or without symptoms in the absence of nonischemic causes
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a prior myocardial infarction

<u>Silent myocardial infarction:</u>

Definition of relevant ECG abnormalities related to silent MI is the presence of:
Its definition is based on the global MI guidelines currently described as the presence in the ECG of:

- Any Q-wave in leads V2-V3 ≥0.02 seconds or QS complex in leads V2 and V3.
- Q-wave ≥0.03 seconds and 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF).
- R-wave ≥0.04 seconds in V1-V2 and R/S ≥1 with a concordant positive Twave in the absence of a conduction defect.

An MI will only be classified as silent if 1) the ECG criteria's are fulfilled, 2) the ECG changes were absent from baseline or previous ECGs and 3) no preceding clinical history of MI (including stent thrombosis and other coronary events) during study follow-up occurred and 4) investigator reporting of silent MI.

Stroke and Transient ischemic attack

Stroke (ischemic stroke and intracranial haemorrhage)
Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

Classification:

A. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

1. Lacunar/Small Vessel (acute infarction in the deep white or gray matter of the cerebrum including the thalamus,mid pons, or deep cerebellum, less than 2 cm on MRI or 1.5 cm on CT scan).
2. Large vessel Atherosclerosis: Infarction distal to >50% luminal stenosis of a cervical or intracranial artery as revealed by MRA, CTA or ultrasound.
3. Cardioembolism: Stroke attributed to embolism form the chambers or valves of the heart
4. Undetermined source:
   a. Undetermined due to incomplete evaluation
   b. Undetermined due to multiple possible causes
   c. Undetermined after complete evaluation (embolic stroke of undetermined source)
   d. Other

B. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

1. Intraparenchymal
   a. Lobar
   b. Deep
   c. Unable to determine
2. Intraventricular expansion
3. Intraventricular
4. Subarachnoid
5. Unable to determine

C. Unclassified Stroke

Unclassified stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B.

Stroke Disability
The Modified Rankin Scale (MRS) will be used to assess stroke outcome. The scale consists of grades, from 0 to 6, with 0 corresponding to no symptoms and 6 corresponding to dead. Investigators will measure and score the MRS based on an interview with the patient at the next regular on-site visit after the onset of the stroke. In those cases where MRS assessment occurred within 90 days after the stroke, a repeat MRS-assessment should be performed at the

next on-site visit.

Modified Rankin Scale

Scale	Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Transient Ischemic Attack (TIA)

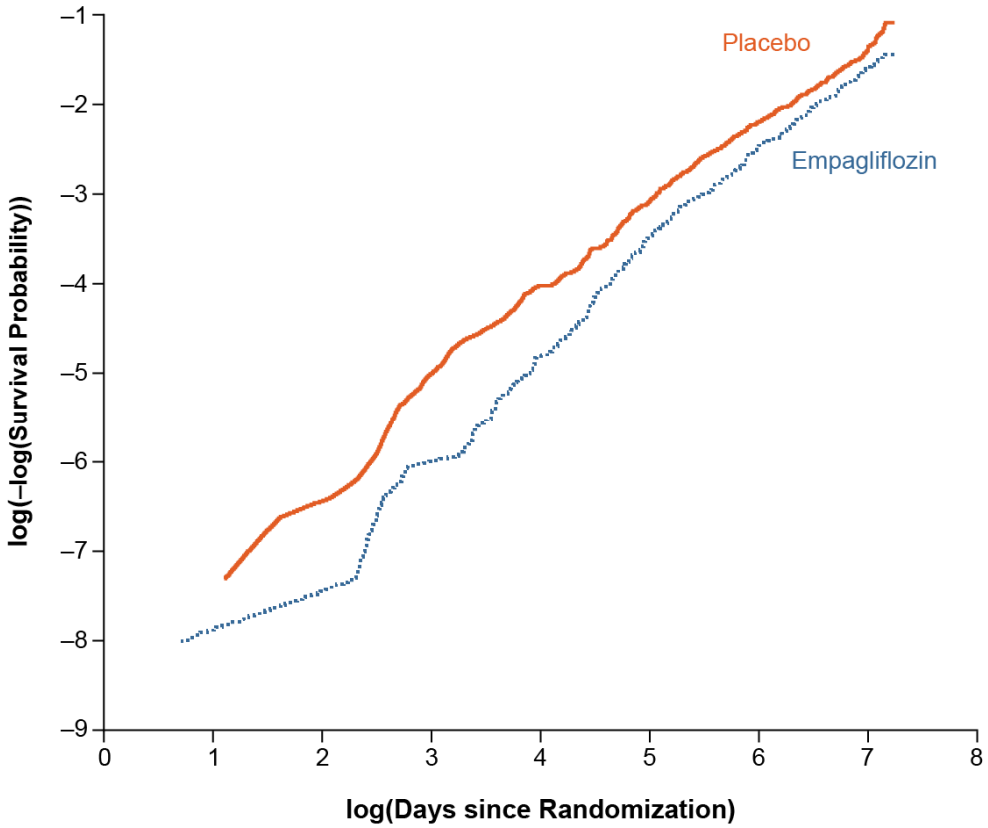
Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, *without* acute infarction.

ASSESSMENT OF THE PROPORTIONAL-HAZARDS ASSUMPTION

The proportional hazards assumption was explored for the primary outcome by plotting log (-log (survival function)) against the log of time by treatment group and checked for parallelism. In addition, an interaction of treatment with log of time was included in the Cox regression model for an exploratory analysis.

The interaction of treatment with log of time showed a p-value of 0.0299. The plot of log (-log (survival function)) against the log of time by treatment group showed minor deviations from parallel curves with a slight convergence over time. However, the curves remain separate throughout the trial.

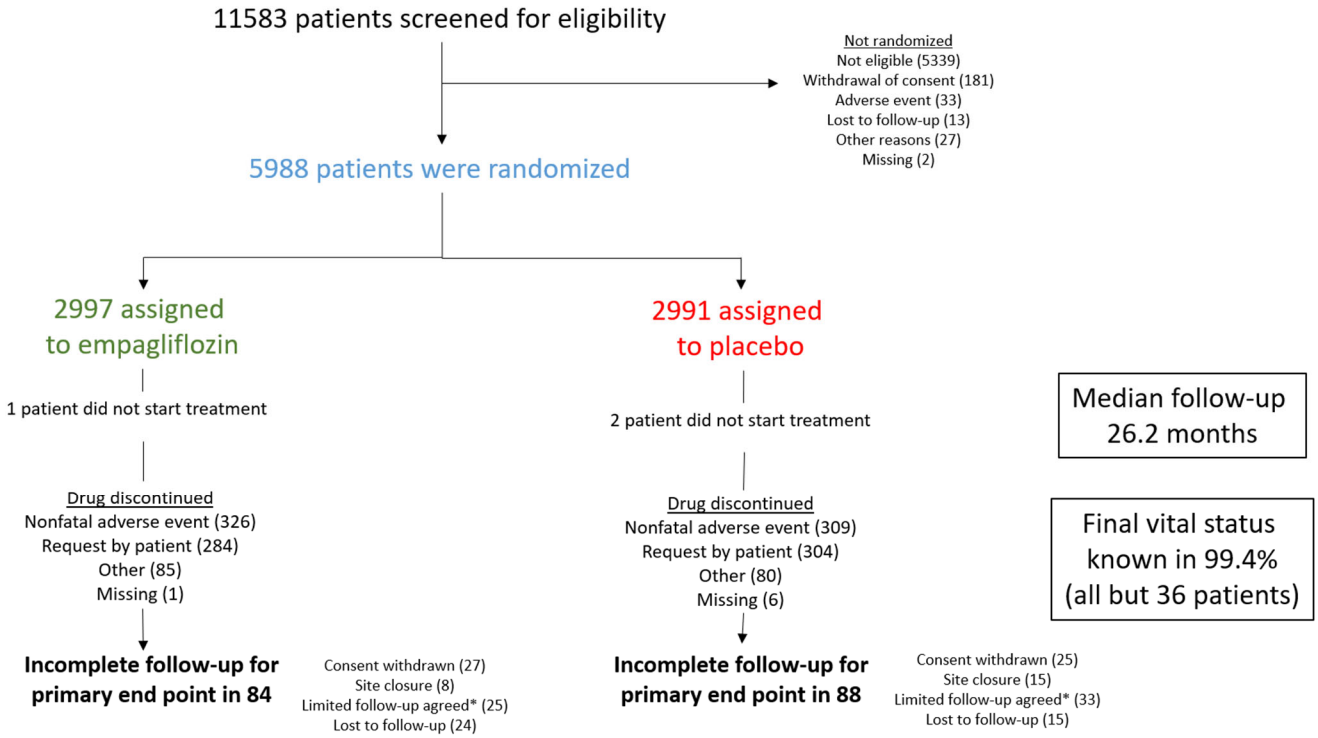
Based on these assessments, the proportional hazards assumption is reasonable with no relevant deviations.



Plot of log (-log (survival function)) against the log of time by treatment group for the primary endpoint.

SUPPLEMENTAL FIGURES

FIGURE S1. PATIENT RECRUITMENT AND DISPOSITION (CONSORT DIAGRAM)



Incomplete follow-up for the primary end point refers to incomplete information on either vital status or hospitalization until the planned end of the treatment period for those patients who had not experienced an adjudicated primary outcome. The 36 patients without known vital status at the end of the trial included 17 on empagliflozin and 19 on placebo. Five patients with missing vital status at the end of the trial experienced an adjudicated hospitalization for heart failure and are not considered to have incomplete follow-up for the primary endpoint. Asterisk denotes patients who discontinued study medication before the trial end but agreed to collection of vital status data at trial completion.

FIGURE S2. PRIMARY COMPOSITE ENDPOINT, ACCORDING TO REGION AND ETIOLOGY OF HEART FAILURE

Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Region			
North America	64/360	83/359	0.72 (0.52–1.00)
Latin America	105/758	120/757	0.87 (0.67–1.13)
Europe	165/1346	202/1343	0.80 (0.65–0.98)
Asia	45/343	69/343	0.59 (0.41–0.86)
Other	36/190	37/189	1.02 (0.64–1.61)
Cause of heart failure			
Ischemic	157/1079	177/1038	0.85 (0.69–1.06)
Non-ischemic	258/1917	334/1953	0.75 (0.64–0.89)

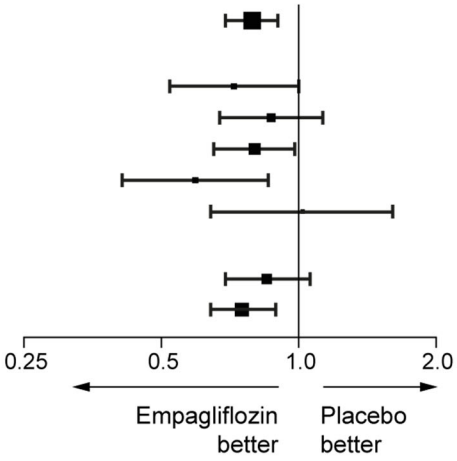
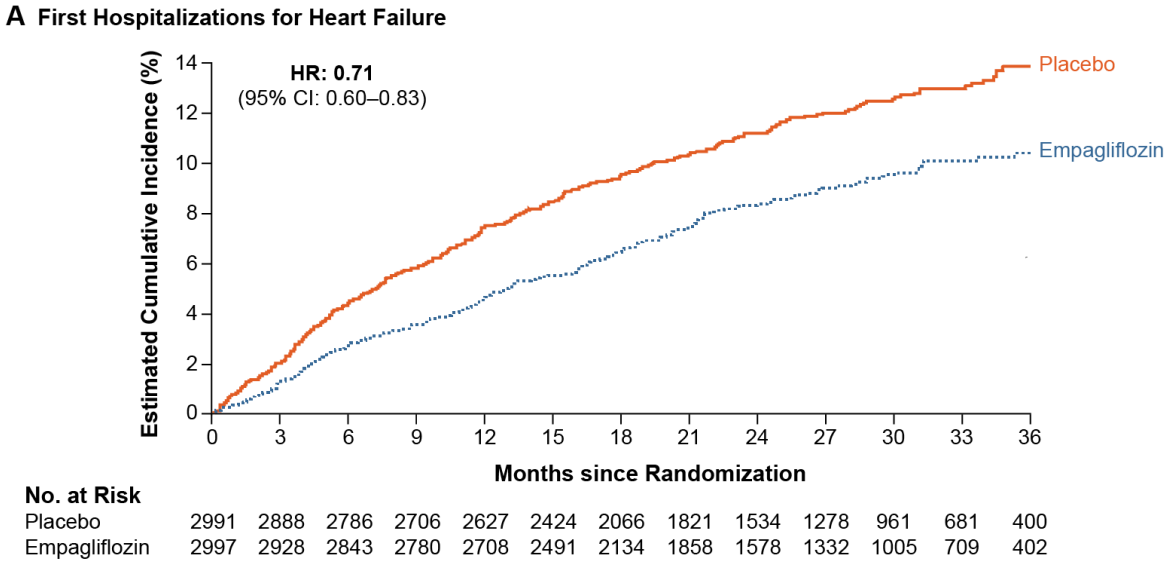


FIGURE S3. COMPONENTS OF THE PRIMARY ENDPOINT

Panel A. First Hospitalizations for Heart Failure. Panel B. Cardiovascular Death.

The estimated cumulative incidence of the two components of the primary end point in each of the two randomized study groups is shown.



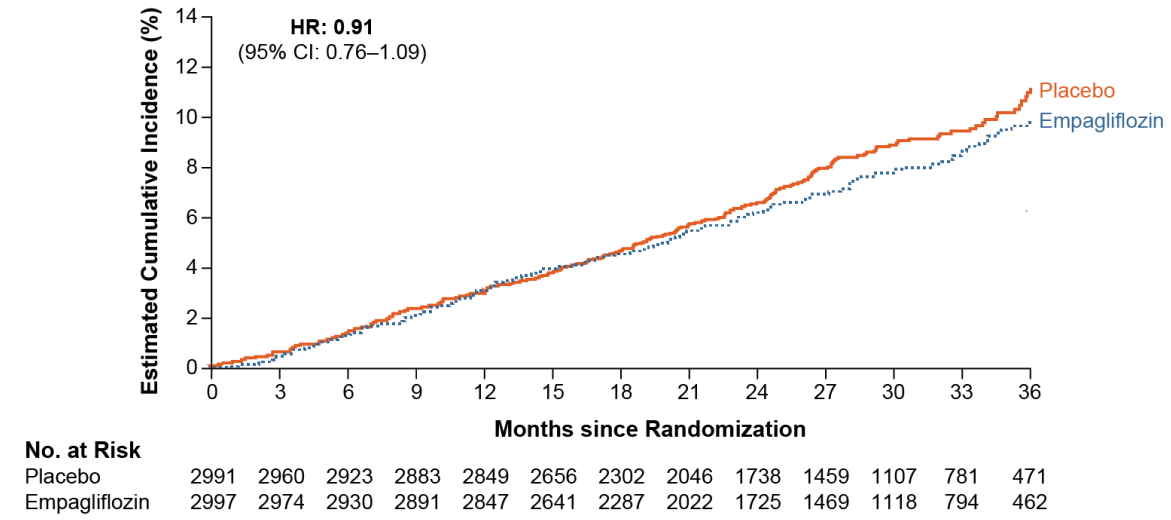
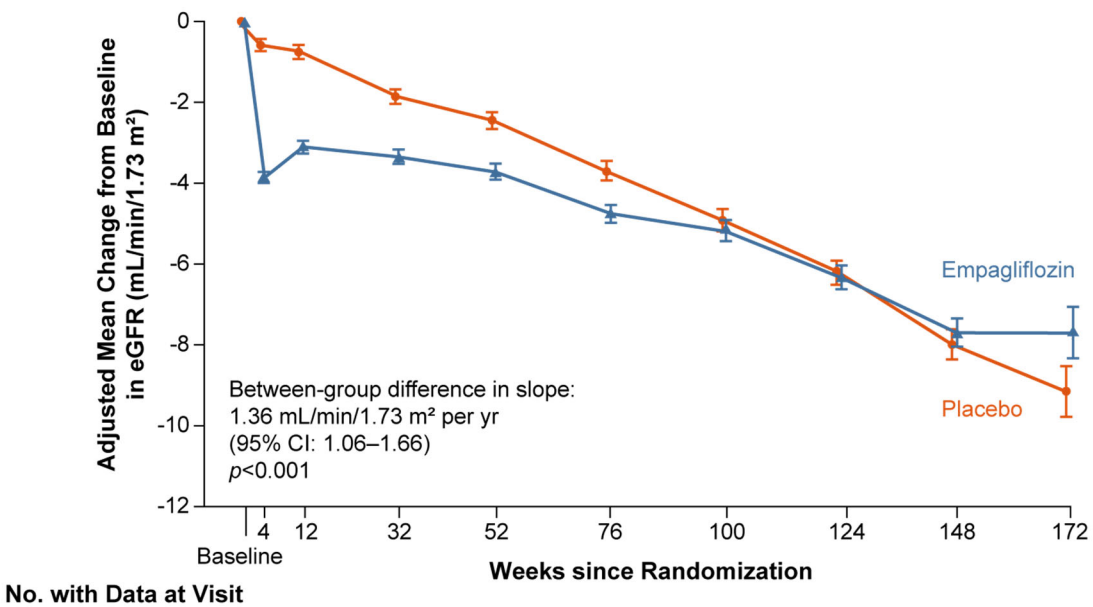


FIGURE S4. CHANGES IN ESTIMATED GLOMERULAR FILTRATION RATE DURING DOUBLE-BLIND THERAPY

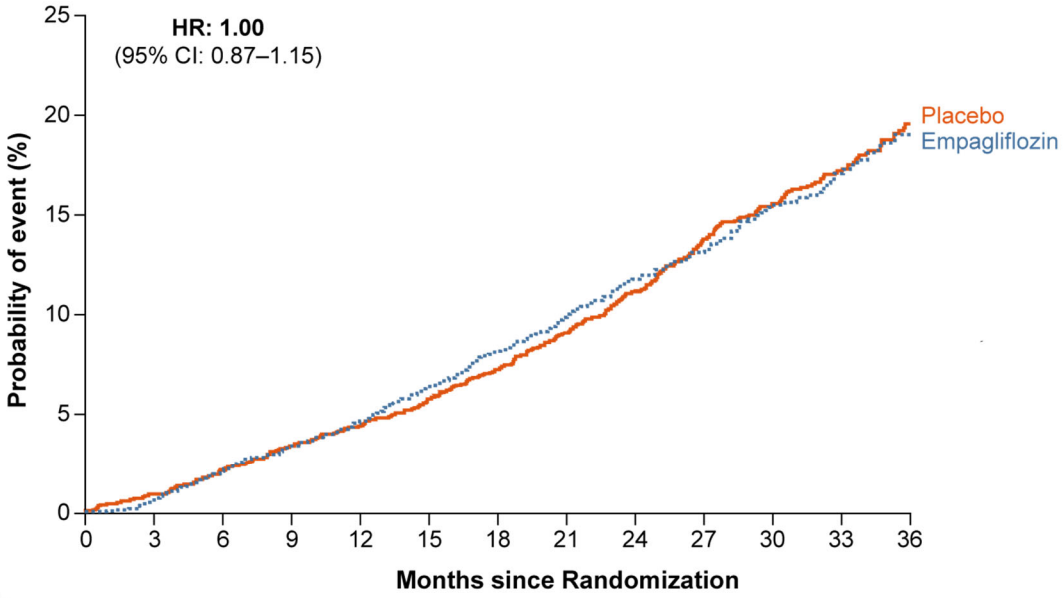


No. with Data at Visit

Placebo	2911	2887	2759	2488	2333	1996	1443	1014	637	209
Empagliflozin	2925	2893	2785	2521	2343	1970	1431	1039	620	212

The adjusted mean changes from baseline in the estimated GFR are shown, as calculated with the Chronic Kidney Disease Epidemiology Collaboration equation. The I bars indicate the standard error. The on-treatment data were analyzed with the use of a mixed model for repeated measures that included age, baseline estimated GFR and left ventricular ejection fraction as linear covariates and sex, region, baseline diabetes status, last projected visit based on dates of randomization and trial closure, baseline estimated GFR according to visit, and visit according to treatment interactions as fixed effects. A different model was used to analyze the slope of the change in the estimated GFR during double-blind treatment, as described in Table 2.

FIGURE S5. ALL-CAUSE MORTALITY



No. at Risk													
Placebo	2991	2960	2923	2883	2849	2656	2302	2046	1738	1459	1107	781	471
Empagliflozin	2997	2974	2930	2891	2847	2641	2287	2022	1725	1469	1118	794	462

SUPPLEMENTAL TABLES

TABLE S1. REASONS THAT SCREENED PATIENTS WERE NOT RANDOMIZED

	Total, N (%)
Number of patients screened	11583
Number of patients not randomized	5595 (100.0)
Adverse event	33 (0.6)
Lost to follow-up	13 (0.2)
Consent withdrawn (not due to adverse event)	181 (3.2)
Inclusion / exclusion criteria not met*	5339 (95.4)
Criteria for NT-proBNP not met	4353 (77.8)
Criteria on ejection fraction not met	266 (4.8)
Any other clinical condition unsafe for participation that would jeopardize patient safety while participating in this clinical trial	200 (3.6)
Renal insufficiency or renal impairment	91 (1.6)
Patient with unstable conditions	74 (1.3)
Conditions on heart failure not met	64 (1.1)
Patients with cardiomyopathies as defined in the protocol	62 (1.1)
No chronic heart failure or not NYHA class II-IV	55 (1.0)
Hemoglobin at screening out of range	53 (0.9)
Indication of liver disease	42 (0.8)
Systolic blood pressure out of range	33 (0.6)
Documented or active malignancy	21 (0.4)
Atrial fibrillation or atrial flutter with a resting heart rate >110bpm	18 (0.3)
Implanted CRT	16 (0.3)
Relevant alcohol or drug abuse and other conditions affecting study compliance	11 (0.2)
Any severe (obstructive or regurgitant) valvular heart disease or any valvular disease expected to lead to surgery during the trial in the opinion of the investigator	8 (0.1)
Age out of range of eligibility	6 (0.1)
History of ketoacidosis	6 (0.1)
Specific inclusion criterion for women of child−bearing potential not met	6 (0.1)
Gastrointestinal (GI) surgery or GI disorder that could interfere with study medication absorption in the investigator´s opinion	6 (0.1)
Treatment with any SGLT2 inhibitor	4 (0.1)
Informed consent too late	2 (<0.1)
Recently implanted ICD	1 (<0.1)
Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial	1 (<0.1)
Specific inclusion criterion for premenopausal women not met	1 (<0.1)
Treatment with any SGLT−2 inhibitor or SGLT−1 and 2 inhibitor	
Intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial	1 (<0.1)
Known allergy or hypersensitivity to empagliflozin	1 (<0.1)
Missing	72 (1.3)
Other	27 (0.5)
Missing	2 (<0.1)

* Patients may have had more than one reason for exclusion. Abbreviations: NT-proBNP = N-terminal prohormone B-type natriuretic peptide; NYHA= New York Heart Association; SGLT2 = sodium-glucose cotransporter 2; ICD = implantable cardioverter-defibrillation; CRT= cardiac resynchronization therapy.

TABLE S2. CARDIOVASCULAR MEDICATIONS AT BASELINE

Type of medication — number (%)	**Empagliflozin** (n=2997)	**Placebo** (n=2991)
Inhibitor of renin-angiotensin system with or without neprilysin inhibitor	2428 (81.0)	2404 (80.4)
Sacubitril/valsartan	65 (2.2)	69 (2.3)
Mineralocorticoid receptor antagonist	1119 (37.3)	1125 (37.6)
Beta blocker	2598 (86.7)	2569 (85.9)
Digitalis glycosides	293 (9.8)	263 (8.8)
Aspirin	1240 (41.4)	1272 (42.5)
Statins	2042 (68.1)	2089 (69.8)

Inhibitors of the renin-angiotensin system include angiotensin converting-enzyme inhibitors and angiotensin receptor blockers.

TABLE S3. CAUSES OF DEATH

	Empagliflozin (n=2997) N (%)	**Placebo** (n=2991) N (%)
Death	422 (14.1)	427 (14.3)
Cardiovascular cause	219 (7.3)	244 (8.2)
Sudden cardiac death	99 (3.3)	114 (3.8)
Heart failure	40 (1.3)	51 (1.7)
Stroke	19 (0.6)	20 (0.7)
Acute myocardial infarction	5 (0.2)	5 (0.2)
Cardiovascular procedures	7 (0.2)	2 (0.1)
Cardiovascular hemorrhage	0	1 (<0.1)
Other cardiovascular causes	16 (0.5)	20 (0.7)
Undetermined cause of death	33 (1.1)	31 (1.0)
Non-cardiovascular cause	203 (6.8)	183 (6.1)
Infection (includes sepsis)	91 (3.0)	78 (2.6)
Malignancy	39 (1.3)	34 (1.1)
Gastrointestinal causes	12 (0.4)	4 (0.1)
Trauma	13 (0.4)	2 (0.1)
Renal causes	4 (0.1)	10 (0.3)
Pulmonary causes	6 (0.2)	5 (0.2)
Hemorrhage	3 (0.1)	3 (0.1)
Hepatobiliary causes	2 (0.1)	3 (0.1)
Neurological (noncardiovascular)	4 (0.1)	0
Suicide	1 (<0.1)	3 (0.1)
Noncardiovascular procedure or surgery	3 (0.1)	1 (<0.1)
Pancreatic causes	0	1 (<0.1)
Other noncardiovascular causes	25 (0.8)	39 (1.3)

TABLE S4. SENSITIVITY ANALYSES FOR THE KEY SECONDARY ENDPOINT

Sensitivity analyses for total hospitalisation for heart failure (HHF)

Analysis	Hazard ratio or rate ratio (95% CI)	P value
Joint frailty model considering CV death as competing risk (primary analysis model)	0.73 (0.61 – 0.88)	< 0.001
Parametric joint gamma frailty model considering CV death as competing risk	0.73 (0.61 – 0.88)	
Joint frailty model considering all-cause mortality as competing risk	0.75 (0.62 – 0.90)	
Negative binomial model*	0.73 (0.60 – 0.89)	
Negative binomial model without covariate adjustment*	0.74 (0.61 – 0.90)	
Cox regression for time to first adjudicated HHF	0.71 (0.60 – 0.83)	

*Rate ratio is shown.
If not stated otherwise, all analyses are adjusted for same covariates as the primary analysis model.
CV = cardiovascular, HHF= hospitalization for heart failure

TABLE S5. SECONDARY OUTCOMES: LABORATORY AND OTHER MEASUREMENTS

Laboratory and other measurements (adjusted change from baseline to 52 weeks)*

Variable	Empagliflozin	Placebo	Adjusted mean difference / geometric mean ratio (95% CI)
Glycated hemoglobin (%) in patients with diabetes – mean (SE)	– 0.16 ± 0.02	0.03 ± 0.02	– 0.19 (–0.25 to – 0.14)
Hematocrit (%) – mean (SE)	1.94 ± 0.07	– 0.41 ± 0.07	2.36 (2.17 to 2.54)
NT-proBNP (pg/mL) – median (IQR)	-29 (-335 to 263)	-9 (-286 to 322)	0.95 (0.91 to 0.99)
Body weight (kg) – mean (SE)	– 1.39 ± 0.09	-0.11 ± 0.09	– 1.28 (–1.54 to –1.03)
Systolic blood pressure (mm Hg) – mean (SE)	– 1.8 ± 0.3	– 0.6 ± 0.3	– 1.2 (–2.1 to -0.3)
Uric acid (mg/dL)	– 0.90 ± 0.03	– 0.10 ± 0.03	– 0.80 (–0.88 to – 0.72)

*Analyzed using a mixed model for repeated measures including age, baseline eGFR(CKD-EPI)cr and baseline LVEF as linear covariates and baseline score by visit, visit by treatment, sex, region, week reachable, and baseline diabetes status as fixed effects. NT-proBNP was analyzed using a geometric mean ratio because modelling was performed on log-transformed data, median (IQR) changes are descriptive. The number of patients with available measurements at week 52 in Empagliflozin/Placebo groups: glycated hemoglobin in patients with diabetes: 1177/1186, Hematocrit: 2425/2418, NT-proBNP: 2477/2460, Body weight: 2516/2497, Systolic blood pressure: 2501/2476, Uric acid: 2447/2429. IQR= interquartile range; SE= standard error of the mean.

TABLE S6. SELECTED ADVERSE EVENTS OF INTEREST

	Empagliflozin (n=2996) N (%)	**Placebo** (n=2989) N (%)
Patients with any adverse event	2574 (85.9)	2585 (86.5)
Patients with any serious adverse event	1436 (47.9)	1543 (51.6)
Selected adverse events of interest		
Hypotension	311 (10.4)	257 (8.6)
Symptomatic hypotension[a]	197 (6.6)	156 (5.2)
Acute renal failure	363 (12.1)	384 (12.8)
Ketoacidosis[b]	4 (0.1)	5 (0.2)
Hepatic injury	115 (3.8)	155 (5.2)
Hypoglycemic events[c]	73 (2.4)	78 (2.6)
In patients with diabetes mellitus	63 (4.3)	66 (4.5)
In patients without diabetes mellitus	10 (0.7)	12 (0.8)
Urinary tract infections	297 (9.9)	243 (8.1)
Complicated urinary tract infections	57 (1.9)	45 (1.5)
Genital infections	67 (2.2)	22 (0.7)
Complicated genital infections	8 (0.3)	8 (0.3)
Bone fractures	134 (4.5)	126 (4.2)
Events leading to lower limb amputation[a]	16 (0.5)	23 (0.8)

Shown are adverse events up to 7 days following discontinuation of study medication, but lower limb amputations were shown up to the end of the trial.

[a] Investigator-defined events

[b] All events occurred in patients with diabetes mellitus at baseline

[c] Hypoglycemic AEs with a plasma glucose value of ≤70 mg/dL or that required assistance